UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS GENE THERAPIES, INC. &
NOVARTIS PHARMACEUTICALS CORPORATION,
Petitioner

v.

GENZYME CORPORATION,
Patent Owner.

Case: IPR2023-00608
Patent No. 9,051,542

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Other Authorities

TABLE OF EXHIBITS

Exhibit	Description
2001	Declaration of Katherine A. Helm, J.D., Ph.D. In Support of Motion for Admission *Pro Hac Vice*
2002	[Reserved]
2003	[Reserved]
2004	Declaration of Martin Christopher Davies in Support of Patent Owner's Preliminary Response ("Davies")
2005	Martyn Christopher Davies, Curriculum Vitae
2006	Xie et al., "*Large-Scale Production, Purification and Crystallization of Wild-Type Adeno-Associated Virus-2*," 122 J. Virol. Methods 17 (2004) ("Xie")
2007	J.F. Wright et al., "*Identification of Factors that Contribute to Recombinant AAV2 Particle Aggregation and Methods to Prevent Its Occurrence during Vector Purification and Formulation*," 12 Molecular Therapy 171 (July 2005)
2008	A.E. Smith, "*Gene Therapy: Where Are We*," 354 The Lancet SI1 (July 1999)
2009	J.O. Konz et al. "*Development of a Purification Process for Adenovirus: Controlling Virus Aggregation to Improve the Clearance of Host Cell DNA*," 21 Biotechnol. Prog. 466 (2005) ("Konz")
2010	Stipulation and Order to Amend Case Schedule, *Genzyme Corp. et al. v. Novartis Gene Therapies et al.*, C.A. No. 21-1736-RGA, D.I. 151 (D. Del.)
2011	October 11, 2022 Defendants' First Amended Invalidity Contentions in *Genzyme Corp. et al. v. Novartis Gene Therapies et al.*, C.A. No. 21-1736-RGA (D. Del.)
2012	June 2023 DocketNavigator Time to Trial Statistics in Patent Cases in the United States District Court for the District of Delaware
2013	Federal Judicial Caseload Statistics 2022
2014	Order Denying Plaintiffs' Motion for Leave to File the Second Amended Complaint, *Genzyme Corp. et al. v. Novartis Gene Therapies et al.*, C.A. No. 21-1736-RGA, D.I. 147 (D. Del.)
2015	Disclaimer in Patent Under 37 CFR 1.321(a) of claims 1 and 2 of U.S. Patent No. 9,051,542

I. INTRODUCTION

Petitioners, Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation ("Novartis") filed two *Inter Partes* Review ("IPR") petitions challenging claims 1, 2, 5 and 6 (the "challenged claims") of U.S. Patent No. 9,051,542 (Ex. 1001, the "'542 patent") as obvious.[1] Both petitions are devoid of the most basic legal and factual proofs required to establish, by a reasonable likelihood, that the challenged claims are obvious.

The '542 patent claims the results of a breakthrough in recombinant adeno-associated virus ("rAAV") compositions for gene therapy made nearly twenty years ago by inventors at Avigen, a small biotechnology company. Administering rAAV vectors to patients for delivery to the central nervous system ("CNS") requires "small volumes of highly concentrated vector." Ex. 1001, 2:12-14. Development of concentrated rAAV compositions was hindered by rAAV particle aggregation, which caused loss of infectivity, biodistribution issues, and adverse immune responses. *Id.*, 2:15-39. Without an adequate solution to the

[1] Novartis also filed a parallel petition, IPR2023-00609, challenging claims 1, 2, 5, and 6 of the '542 patent, and Genzyme Corporation ("Genzyme") concurrently files its Preliminary Response to IPR2023-00609 and its Response to Petitioners' Notice Regarding Multiple Petitions.

problem of rAAV aggregation, gene therapy formulations would be ineffective and unviable. Ex. 2008, SI2 ("[H]igh doses of viral vector … are usually required to achieve measurable gene transfer"); Ex. 2007, 171; Ex. 1005 ("Huang"), S286. While this problem and its severity was documented, the '542 patent inventors were the first to solve it. They surprisingly discovered that significant aggregation could be prevented by formulating compositions with an ionic strength greater than 200 mM. *Id.*, 7:1-21. The inventors' innovation further allows the compositions to be isotonic and suitable for human parenteral administration by including the use of multivalent ions to increase ionic strength. *Id.*, 7:1-8.

In its Petition, Novartis stitches together its case for obviousness for individual claim elements by relying wholly and impermissibly on hindsight, while failing to address the claimed combination. Novartis selectively picks and chooses piecemeal art to cobble together the disclosure for each element, while ignoring that the field as a whole would not have led the person of ordinary skill in the art ("POSA")[2] to the claimed combination. ***First***, it is black letter law that establishing obviousness requires the evaluation of a claim as a whole to guard against "hindsight reasoning, using the invention as a roadmap to find its prior art

[2] For this Preliminary Response only, Genzyme does not challenge Novartis's definition of the POSA. Petition, 16-17 (citing Amiji, ¶82).

components." *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). ***Second***, it is a "longstanding principle that the prior art must be considered for all its teachings, not selectively." *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019).

Genzyme has now disclaimed claims 1 and 2, so only claims 5 and 6 remain challenged. 37 C.F.R. § 42.107(e).[3] Ground 2 addresses only now disclaimed claim 2, and thus, need not be considered. Remaining Grounds 1 and 3 each fail to identify how the prior art would have motivated or given the POSA any reason to develop highly concentrated rAAV compositions having elevated ionic strength without significant aggregation. For example, Novartis alleges that the POSA would have been motivated to increase the ionic strength of prior art compositions disclosed in the primary reference of Ground 1, Evans (Ex. 1003)—cited by the Examiner multiple times as "pertinent art" (Ex. 1002, 191, 224, 321)—and Ground 3, Frei (Ex. 1004), by adding sodium chloride ("NaCl") to the disclosed compositions. But Novartis's argument ignores that both Evans and Frei teach that *lower* NaCl concentrations improve stability for their disclosed compositions, and

[3] Claims 1 and 2 were disclaimed to streamline issues for the Board, because only claims 5 and 6 are asserted for infringement in the co-pending litigation.

neither suggests that increasing NaCl concentration prevents aggregation. Frei, in fact, emphasized the "***threat to stability posed by the high salt concentrations***" in certain of its compositions. Frei, 19:12-14.[4]

Testimony by Novartis's expert, Dr. Amiji, further exposes the hindsight bias of Novartis's arguments. Novartis's motivation arguments depend on the premise that the POSA would have been motivated to develop compositions for "human parenteral administration." Petition, 18, *see also id.*, 1, 7, 12, 19, 25, 31, 33, and 52. For Ground 1, however, the NaCl concentrations that Novartis alleges the POSA would have been motivated to select from the prior art are so high that, according to Dr. Amiji, they would have been expected to potentially cause "tissue damage and injection pain" in patients. *Infra* § IV.A.2.b.iii (quoting Amiji, ¶131).

Novartis also does not provide a basis for the POSA to have reasonably expected that a composition having the claimed rAAV concentration and ionic strength would suppress aggregation—no cited reference teaches or suggests preventing aggregation in a high-concentration rAAV composition with high ionic strength. Claims 5 and 6 require, respectively, that the composition does not exhibit significant aggregation as determined by particle radius (claim 5) and percent product recovery following filtration (claim 6). Novartis argues that these

[4] Emphases are added unless otherwise stated.

elements are merely "inherent characteristics" of the claimed composition (Petition, 41-42, 44, 60), but fails to provide prior art or testing evidence to support its inherency arguments. To prove inherency in the context of obviousness "[a] party must … meet a high standard … the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *PAR Pharm., Inc. v. TWI Pharms., Inc*., 773 F.3d 1186, 1195-96 (Fed. Cir. 2014).

Finally, institution should be denied as a matter of discretion under the Board's precedent in *Fintiv*/*NHK*. In December 2021, Patent Owner, Genzyme filed suit against Novartis for infringement of several patents by Novartis's Zolgensma®. On February 23, 2022, Genzyme amended its complaint to assert the '542 patent. Novartis filed this Petition nearly a year later—one day before the expiration of its one-year § 315(b) bar. Petition, 67-68. Meanwhile, the litigation has significantly progressed—the district court completed its claim constructing hearing, invalidity and infringement contentions have been exchanged, and fact discovery closes on June 30, 2023. Opening expert reports will be served on August 4, 2023 before an institution decision is due, a jury trial is scheduled for March 2024, and the Court has expressly opposed delays. Instituting this IPR would be highly inefficient, with a district court trial occurring approximately six months ***before*** a Final Written Decision. Notwithstanding the unmistakable

relevance of *Fintiv*, the Petition does not even mention it and Novartis has not proffered a stipulation of any kind, much less a *Sotera* stipulation.

Novartis fails to establish a reasonable likelihood of succeeding in this Petition, much less that compelling merits favor institution as required under the Board's *Fintiv* standard. The Board should deny institution.

II. THE '542 PATENT

The inventors were able to overcome the challenge of concentration-induced rAAV aggregation, while also ensuring the resulting rAAV composition would be suitable for human parenteral administration (Ex. 1001, 5:10-20), including considerations of tonicity, pH, and the pharmaceutical acceptability of excipients, which elevated the complexity of solving the rAAV aggregation problem.

A. Disclosed Innovation

After many unsuccessful attempts at solving AAV aggregation, the inventors discovered that high ionic strength was the key to storable compositions suitable for human administration. Ex. 1001, Abstract (The '542 patent discloses "high ionic strength solutions…that are nonetheless isotonic with the intended target tissue…achieved using salts of high valency"). The inventors studied vector aggregation in solutions of sodium chloride, sodium citrate, sodium phosphate, sodium sulfate, magnesium sulfate, and glycerol, and tracked aggregation as a

function of two parameters, osmolarity (Figure 1A) and ionic strength (Figure 1B). *Id.*, 6:63-65, 12:33-67 (Example 3), FIGS. 1A, 1B.

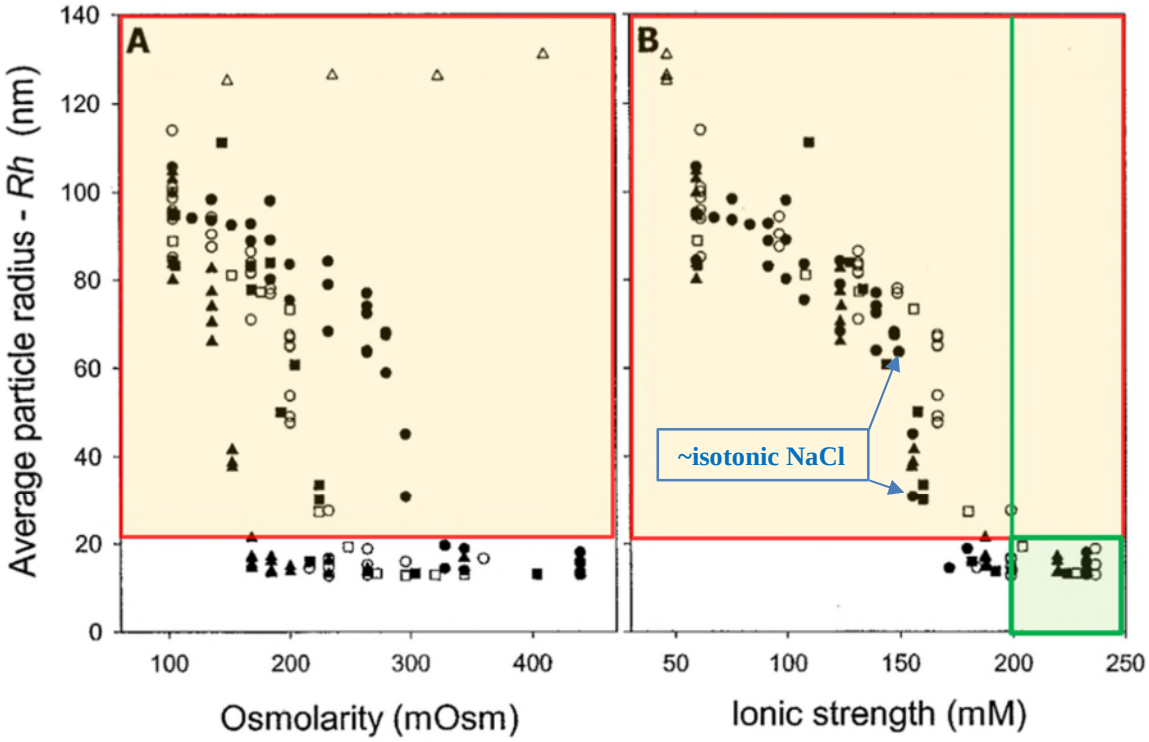
Osmolarity is a measure of the number of particles of solute per liter. For a salt that fully dissociates like NaCl there are two solute particles, one Na^+ and one Cl^-, for every equivalent of NaCl. Ex. 2004 ("Davies"), ¶¶29-37 (citing Ex. 1020, 614). Therefore, the osmolarity of NaCl, expressed in osmols, is double its molarity. *Id.*, ¶¶32, 59. For magnesium chloride ($MgCl_2$), which contains three particles of solute, one Mg^{2+} and two Cl^- ions, the osmolarity is triple the molarity of $MgCl_2$. *Id.*, ¶¶33, 59.

"Ionic strength is a measure of the intensity of the electrical field in a solution" and it increases exponentially as a function of an ions charge. *Id.*, ¶38. (citing Ex. 1020, 616). A 100 mM NaCl solution has an osmolarity of 200 mOsm and an ionic strength of 100 mM, whereas a 100 mM $MgCl_2$ solution has an osmolarity of 300 mOsm and an ionic strength of 300 mM. *Id.*, ¶¶39-40. This illustrates that the ionic strength of multivalent ion-containing salts (*e.g.*, $MgCl_2$) is higher per osmol than salts of monovalent ions (*e.g.*, NaCl).

In Figures 1A and 1B, "[a]verage particle radius is measured by dynamic light scattering (DLS) following vector dilution in varying concentrations of excipients buffered with 10 mM sodium phosphate at pH 7.5." Ex. 1001, 4:18-21. Given the average radius of these viral particles is approximately 13 nm, "Rh

values >20 nm are deemed to indicate the occurrence of some level of aggregation." *Id.*, 9:25-27; Davies, ¶¶44-47.

In annotated Figures 1A and 1B below, the excipients are denoted as follows: sodium chloride (●), sodium citrate (◯), sodium phosphate (▪), sodium sulfate (□), magnesium sulfate (▲), and glycerol (Δ):



Id., FIGS. 1A, 1B (annotation added). In both Figures, compositions falling within the orange shaded portion of the plots exhibited significant aggregation (Rh > 20 nm), whereas compositions in the unshaded or green shaded portions of the plot did not (Rh < 20 nm).

The results of Figure 1A, which plots particle radius as a function of osmolarity, showed no consistent relationship between aggregation and osmolarity

across the tested excipients. At the extremes, "magnesium sulfate [(▲)] prevented aggregation at >200 mOsm whereas sodium chloride [(●)] required ≧350 mOsm to achieve a similar effect," while glycerol (Δ) never prevented aggregation even at >400 mOsm. *Id*., FIG. 1A, 7:1-8 (Stating that "[s]odium citrate, sodium sulfate, and sodium phosphate are intermediate in their potency to prevent vector aggregation").

Figure 1B shows data from the same experiment "plotted as a function of the calculated ionic strength, rather than osmolarity, for each excipient." *Id.*, 7:18-20. In contrast to Figure 1A's particle radius versus osmolarity plot, Figure 1B's plot of particle radius versus ionic strength shows a clear trend; "vector aggregation is prevented when ***ionic strength is ~200 mM or greater*** regardless of which salt is used" as shown by the green line at 200 mM ionic strength in annotated Figure 1B, above. *Id.*, 7:21-22. These data led to the breakthrough "that the ionic strength (μ) of a solution … is the ***primary factor affecting aggregation***." *Id.*, 7:22-25. The green box in annotated Figure 1B illustrates the scope of claim 5 requiring both an "ionic strength … greater than 200 mM" and a "an average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering." *Id.*, 14:34-37.

The identification of ionic strength as a key to preventing aggregation unlocked the path to isotonic compositions for human parenteral administration by employing multivalent ions to adjust ionic strength. As the inventors observed,

"[o]f practical concern, commonly used buffered saline solutions have insufficient ionic strength to prevent AAV2 vector aggregation at concentrations exceeding 10^{13} particles/mL." *Id.*, 4:65-67. "Isotonic (150 mM) [NaCl] has an ionic strength of 150 mM, a value insufficient to maintain AAV2 solubility at high vector concentrations," as shown in annotated Figure 1B. *Id.*, 5:15-17. Thus, making a concentrated rAAV composition in NaCl would require the formulation to be hypertonic. *Id.*, 5:4-7; Davies, ¶¶34-35, 58.

Because of the exponential relationship between ionic strength and charge valency, "multivalent ions" (*i.e.*, ions having a charge of two or more) "achieve a similar degree of inhibition of aggregation at lower concentrations than monovalent [NaCl]," for which Na^+ and Cl^- only contribute one charge each. *Id.*, 7:1-8. Davies, ¶¶32-33, 58-59. The inventors recognized and capitalized on the "exponential relationship of ionic strength with charge [v]alency … to develop isotonic formulations with high ionic strength." Ex. 1001, 5:7-10. Compositions containing multivalent ions, including pharmaceutically acceptable excipients containing citrate, sulfate, magnesium, and/or phosphate can have an ionic strength of greater than 200 mM, while remaining isotonic or minimizing isotonicity, because multivalent ions even at low concentrations have high ionic strength.

Novartis alleges that the '542 patent "admits" that it was "known that high salt concentrations increase AAV2 vector solubility." Petition, 7 (quoting Ex.

1001, 4:67-5:4); *see also id.* (quoting Ex. 1001, 1:52-55). Novartis, however, ignores that the cited passages of the '542 patent relate to "highly concentrated AAV2 vectors recovered from gradients … in concentrated CsCl" (Ex. 1001, 4:67-5:7) that were understood to be unsuitable for human administration. *Infra* § IV.A.2.b.iv; Davies, ¶106. Thus, as of the priority date the prior art lacked any indication that it was possible to make a storable composition of concentrated rAAV vector particles without significant aggregation, let alone by developing high ionic strength compositions.

Particle size detection *(id.,* 9:5-50 (Table 3), claim 5) and percent product recovery following filtration (*id.*, 7:65-8:40 (Table 2), claim 6), further confirmed that high ionic strength compositions did not exhibit significant rAAV aggregation. The inventors prepared three solutions for AAV2-AADC vectors: "Control Formulation (**CF**: 140 mM sodium chloride, 10 mM sodium phosphate, 5% sorbitol, pH 7.3); Test Formulation 1 (**TF1**: 150 mM sodium phosphate, pH 7.5); and Test Formulation 2 (**TF2**: 100 mM sodium citrate, 10 mM Tris, pH 8.0)." *Id.*, 11:66-12:3. In Experiment 1 the samples contained 2.5×10^{13} vg/ml vector, and in Experiment 2 the samples contained 6.7×10^{13} vg/ml vector. *Id*., 12:4-12.

In Example 2, the exemplary formulations were filtered through a 0.22 μm filter. *Id.*, 8:1-10, 11:53-12:29. Table 2 summarizes the results of Experiments 1 and 2, including the ionic strength of each formulation. *Id.*, 8:19-44.

TABLE 2

AAV VECTOR RECOVERY AT PROCESS SCALE

Experiment	Formulation	μ (mM)	Target (vg/mL)	Actual (vg/mL)	Yield % (RSD)
1	CF	160	2.5E13	1.93E13	77 (6.6)
1	TF1	310	2.5E13	2.38E13	95 (7.4)
1	TF2	510	2.5E13	2.33E13	93 (7.4)
2	CF	160	6.7E13	3.98E13	59 (6.0)
2	TF2	510	6.7E13	6.42E13	96 (4.4)

As Table 2 shows, recoveries exceeded 90% following filtration in formulations TF1 and TF2 having ionic strengths greater than 200 mM, whereas recovery from CF formulations, having ionic strength of 160 mM, was only 77% and 59% for experiments 1 and 2, respectively.

The inventors also conducted storage and freeze-thaw ("F/T") cycle studies on the CF, TF1, and TF2 formulations, with the results presented in Table 3, in which particle radius was measured by DLS to determine the presence of aggregates. *Id.*, 9:5-65.

TABLE 3

STABILITY OF AAV2 VECTORS

	Particle radius - Rh (nm)							
Formu-		4° C.	−20° C.			−80° C.		
lation	Pre	5 d	1 F/T	5 F/T	10 F/T	1 F/T	5 F/T	10 F/T
CF	14.5	27.0	22.4	56.1	94.5	20.6	57.5	141
TF1	13.8	16.3	TH	TH	TH	TH	TH	TH
TF2	13.8	14.4	14.2	14.0	14.1	13.8	21.3	50.9

Pre: DLS radius measured immediately following 0.2 μm filtration.
Vector concentrations (vg/mL): CF: 1.93E13, TF1: 2.38E13, TF2: 2.33E13.
TH: signal intensity is too high to measure because of extensive aggregation.

"As shown in Table 3 … CF shows some aggregation after 5 days …. For vector prepared in TF1, no aggregation occurs after 5 days [of storage] at 4° C …. For vector prepared in TF2, no aggregation is observed at 4° C., or following up to 10 F/T cycles at −20° C …." *Id.*, 9:44-55. These studies further confirmed the importance of increased ionic strength in preventing aggregation. *Id.*, 10:29-43.

B. Challenged Claims

By virtue of their dependence from claim 1, claim 5 and 6 both recite, *inter alia*:

- "purified, recombinant AAV vector particles at a concentration exceeding 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml;"
- "one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate;"
- "the ionic strength of the composition is greater than 200 mM,"
- "the purified AAV vector particles are stored in the composition without significant aggregation."

Claim 5 further recites:

- "the purified, recombinant AAV vector particles have an average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering."

Claim 6 further recites:

- "recovery of the purified, recombinant virus particles is at least about 90% following filtration of the composition of said AAV vector particles through a 0.22 μm filter."

III. CLAIM CONSTRUCTION

For this Preliminary Response only, Genzyme does not challenge the Petition's alleged "plain and ordinary meaning" constructions. Petition, 17.

IV. NOVARTIS FAILS TO ESTABLISH A REASONABLE LIKELIHOOD THAT CLAIMS 5 AND 6 ARE OBVIOUS

Novartis has not established a reasonable likelihood of proving claims 5 and 6 obvious, much less presented compelling merits that claims 5 and 6 are obvious. Novartis fails to meet its burden on all Grounds for at least three claim limitations, each of which constitute an independent basis for denying institution: (1) the rAAV "concentration exceeding $1x10^{13}$vg/ml up to $6.4x10^{13}$vg/ml"; (2) "the ionic strength of the composition is greater than 200 mM" ; and (3) the respective aggregate limitations of claims 5 and 6. The Board should also discretionarily deny institution based on Ground 1 under § 325(d). *Infra* § IV.B

A. Ground 1: The Petition's Combination of Evans, Huang, and Mingozzi Fails to Render Claims 5 and 6 Obvious

Evans does not address the aggregation of adenoviruses, AAV, or any other virus particles, and is instead directed to inhibiting radical oxidation. Evans, 9:23-25 (A "centerpiece of [Evans'] formulations … relate[s] to inclusion of

components that act as inhibitors of free radical oxidation."); *id.*, 13:8-11 ("An essential quality of the present invention is the finding that non-reducing free radical scavengers and/or chelators are important for maximizing both short and long term stability of viral formulations."); Davies, ¶67.

Huang merely highlights the problem of aggregation, stating that "at high concentrations, AAV virions form aggregates of different sizes in a range of different buffer systems and storage conditions. The size of aggregates appears to be concentration dependent." Huang, S286. Huang states "that some of our formulations could lead to a 30-50% ***reduction in the size*** of aggregates," but does not explain what this size reduction means in terms of particle radius or any other metric, does not disclose information about its formulations, and never suggests that its stored rAAV compositions could remain free of significant aggregation. Davies, ¶68.

Mingozzi, like Evans, never addresses aggregation. In fact, Mingozzi does not address rAAV formulation or storage at all. Davies, ¶69.

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. The Petition never establishes that the POSA would have had any motivation or reason to combine Evans, Huang, and Mingozzi in a manner that would have resulted in the compositions of claims 5 and 6. "Failure to

consider the claimed invention as a whole" as Novartis does here "is an error of law." *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984); *see also Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1364 (Fed. Cir. 1998); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1548 (Fed. Cir. 1983).

Novartis bases its motivation argument for Ground 1 on formulating a composition suitable for "human parenteral use." Petition, 25, 31, 33. The POSA, however, would not be motivated to achieve the claimed invention by increasing Evans' NaCl concentration as Novartis argues, because the osmolarity of such a composition would deviate significantly from isotonicity, potentially resulting in "tissue damage and injection pain" upon administration. Amiji, ¶131; Davies, ¶¶34-37. Novartis also fails to establish a reasonable expectation that such a composition would be free of significant aggregation. Further, Novartis does not submit any evidence that the particle radius and product recovery elements of claims 5 and 6, respectively, would inherently result from the claimed combination. Each deficiency is an independent reason that Novartis fails to establish a reasonable likelihood of proving claims 5 and 6 obvious.

1. Evans Does Not Disclose a Composition Having the Claimed Viral Genome Concentration

Novartis cannot support its contention that Evans discloses a composition comprising viral particles at "a concentration exceeding $1x10^{13}$ vg/ml up to $6.4x10^{13}$ vg/ml," as the challenged claims require. Petition, 25, 30; Davies, ¶¶71-

74. The Petition cites Evans's disclosure of "a virus concentration in the range from about $1x10^7$vp/mL to about $1x10^{13}$vp/mL" to argue that the uppermost endpoint of this range ($1x10^{13}$vp/mL ± 5%) overlaps with the scope of the claims, "***[a]ssuming that 100% of the particles contain vector genomes***." Petition, 30 (citing Evans, claim 3).

Novartis provides no basis for why the POSA would make such an assumption. Novartis cites only its expert, Dr. Amiji, who "does not cite to any additional supporting evidence or provide any technical reasoning to support his statement … and is entitled to little weight." *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15 (PTAB Aug. 24, 2022) (precedential).

In fact, Dr. Amiji's declaration indicates that the POSA ***would not have assumed*** that Evans's viral particle compositions were free of empty capsids, and instead would have assumed the opposite—that as many as 90% of capsids in a given composition are empty. Davies, ¶¶72-73. Dr. Amiji states that "Wright [Ex. 1007] teaches that ≥ 10^{14} capsid particles (cp)/ml corresponds to ≥ 10^{13} vg/ml)," indicating as much as ***10-fold excess in empty capsids***. Amiji, ¶119 (citing Ex. 1007, 176).

Similarly, Lochrie (Ex. 1010) states that "***more than 80% of AAV material*** created during rAAV production ***may be empty capsids***." Lochrie, 4:20-23. Evans states that its "recombinant Ad5gag virus was purified by ***column***

chromatography," (Evans, 21:12-13), but Lochrie states "current column chromatography purification techniques do not separate packaged capsids from empty capsids." Lochrie, 4:20-23. Thus, Novartis's own supporting testimony and evidence demonstrate that the POSA would have understood that Evans' compositions would not have contained a vector genome concentration "exceeding $1x10^{13}$ vg/ml" or anything close.

2. Novartis Fails to Provide a Motivation or Reason to Combine Evans, Huang, and Mingozzi to Arrive at the Claimed Composition

a. Novartis Fails to Establish a Motivation to Develop a Composition Having the Claimed rAAV Concentration, Ionic Strength, and One or More Multivalent Ions

Novartis falls prey to "hindsight reasoning" that "discount[s] the value of combining various existing features or principles in a new way to achieve a new result." *Ruiz*, 357 F.3d at 1275. Novartis fails to establish that the POSA would have been motivated to develop a composition comprising an rAAV "concentration exceeding $1x10^{13}$ vg/ml," "one or more multivalent ions selected from … citrate, sulfate, magnesium, and phosphate," with an ionic strength "greater than 200mM." Davies, ¶¶75-79.

Novartis cites Mingozzi to argue that the POSA would been motivated to administer "doses of $3.2x10^{13}$vg for a 60kg human" at a "concentration exceeding $1x10^{13}$ vg/ml." Petition, 31. Mingozzi, however, says nothing about any

formulations for AAV vectors let alone anything about ionic strength or multivalent ions. Davies, ¶78.

As of June 2004, the problem of rAAV aggregation in high concentration compositions was unsolved. Novartis acknowledges and cites references demonstrating that the POSA understood that higher viral particle concentrations caused increased aggregation. Petition, 14-15 (citing Huang, S286); Ex. 1013, 1286 ("High concentrations of protein may induce aggregate formation."); Ex. 1007, 175 ("rAAV undergoes concentration-dependent aggregation."); Davies, ¶¶76-77. Novartis also acknowledges that Huang disclosed that aggregation led to significant losses in infectivity in high concentration rAAV compositions, when compared to lower concentration compositions. Petition, 19, 32 (citing Huang, S286) ("[W]hen the concentration reached 5-10x10^{13}vg/ml, gene transfer efficiency was ***10-100-fold lower*** compared to the same vector administered at the same dose but having a concentration of 1-5x10^{12}vg/ml").

Evans, Huang, and Mingozzi, alone or in combination do not teach or suggest how to make high concentration rAAV compositions without significant aggregation. Novartis never explains "*how* or *why* the references would be combined to produce the claimed invention." *TriVascular, Inc. v. Samuels,* 812 F.3d 1056, 1066 (Fed. Cir. 2016). The inventors were the first to overcome rAAV aggregation at "concentration[s] exceeding 1x10^{13} vg/ml" when they determined

that compositions with an ionic strength of greater than 200 nm did not exhibit significant aggregation. *Supra* §II.A (citing Ex. 1001, Figs. 1A, 1B).

b. Novartis Misapplies Overlapping Range Obviousness Case Law to Arrive at the Claimed Ionic Strength

To reach the claimed ionic strength of greater than 200 mM, Novartis argues that the POSA would have made a composition with nearly the maximum recited amounts of sodium chloride (NaCl) and magnesium chloride ($MgCl_2$) disclosed in Evans. Petition 35 ("Accepting the ***high end of both ranges***, Evans's claim 5 composition comprising 250mM of NaCl and 5mM of $MgCl_2$ has an ionic strength of 265mM.").

Novartis urges the Board to find that the claimed ionic strength range is obvious by citing anticipation case law regarding ranges, "[b]ecause the ionic strength range … ('greater than 200mM') encompasses the ionic strength achieved by an embodiment falling within the scope of Evans's claim 5." Petition, 35-36 (citing *In re Wertheim,* 541 F.2d 257, 267 (CCPA 1976) ("the disclosure in the prior art of any value within a claimed range is an anticipation of the claimed range."). *Wertheim* is inapplicable here, because it pertains to a specific prior art value falling within a claimed range. *Wertheim,* 541 F.2d at 267 ("Pfluger 1963 teaches fragmenting the frozen foam into 3/4-inch pieces before drying; 3/4 inch is, of course, 'at least 0.25 mm.'"); *see also Atofina v. Great Lakes Chem. Corp.*, 441

F.3d 991, 1000 (Fed. Cir. 2006) ("The disclosure of a range … does not constitute a specific disclosure of the endpoints of that range.").

For a range to be obvious, a parameter must first be recognized as a "result-effective variable," before the determination of the optimum or workable ranges of that variable might be characterized as routine experimentation. *See In re Antonie*, 559 F.2d 618, 620 (CCPA 1977). Novartis fails to identify any disclosure in Evans, Huang, and/or Mingozzi suggesting that ionic strength would impact rAAV aggregation.

i. Novartis Fails to Demonstrate that Ionic Strength Was a Recognized Result Effective Variable

Novartis argues that a "POSA would have been motivated to select the 'high end' concentration of NaCl and $MgC1_2$ in Evans "because ionic strength was a known condition that likely affects vector aggregation." Petition, 36 (citing Ex. 1007, 175; Amiji, ¶¶175-177). Novartis, however, mischaracterizes Wright (Ex. 1007) to support its contention that "ionic strength … likely affects vector aggregation." Wright stated that the "mechanism of vector aggregation is ***not well understood***, and purification conditions that ***may affect aggregation include*** buffer ionic strength and pH, shear and vector concentration." Ex. 1007, 175. Novartis never explains how Wright's statement that factors causing vector aggregation were "not well understood"—followed by a non-exclusive list of conditions that

may impact aggregation—was an indication that "ionic strength … ***likely*** affects vector aggregation." *Id.*; Davies, ¶¶80-81.

Moreover, the POSA would have understood that adjustments to *buffer* ionic strength would not be made by adding salts such as NaCl or $MgCl_2$. Davies, ¶¶41-42, 81-84. Buffers, which are added to modify and maintain a target pH, have their own intrinsic buffer ionic strengths. Ex. 1020, 225. For example, "50mM sodium phosphate containing 0.1M NaCl, [is] a buffer that has a relatively high ionic strength" where phosphate provides the buffering effect. Ex. 1018, 32. A "buffer of moderate ionic strength" is "10mM Tris, pH 8.5, 100 mM NaCl, l mM EDTA" (*id.*, 33), where Tris and EDTA provide the buffering effect. Both the moderate and high ionic strength buffer solutions have the same NaCl concentrations (0.1 M = 100 mM), so the difference in their ionic strengths comes from the buffering species, not NaCl. Davies, ¶¶41-42, 83.

Moreover, Wright's adenovirus formulation contains only 25 mM NaCl (Ex. 1007, 176), which is 10-fold below the 250 mM NaCl concentration Novartis alleges was obvious. Thus, Wright also fails to teach or suggest ionic strength as a results-effective variable for rAAV aggregation. Davies, ¶¶84-85.

ii. Novartis Fails to Account for the Totality of Evans' Teachings

Novartis's motivation argument ignores Evans' teachings as a whole. *Henny Penny*, 938 F.3d at 1332 (reiterating "the longstanding principle that the prior art

must be considered for all its teachings, not selectively."); *W.L. Gore*, 721 F.2d at 1551 (holding that a prior art reference must be considered in its entirety, including portions leading away from the claimed invention). Evans does not contain any disclosure regarding particle aggregation. Novartis also omits that Evans conducted stability testing only on formulations having viral particle concentrations ranging from 10^7 to 10^{11} vp/ml—several orders of magnitude below the 10^{13} vp/ml upper limit of Evans' concentration range, which itself is an order of magnitude below the claimed $1x10^{13}$ vg/ml concentration (expressed in vector genomes/ml as opposed to viral particles/ml). Evans, 24:21-22 and 25:14-15 (Example 2), 25:31-32 and 26:3-4 (Example 3), 29:6 (Example 7), 30:14 (Example 9); Davies, ¶86.

Novartis's argument that the POSA would have been motivated to "select the high end of the concentration ranges for NaCl and $MgCl_2$ in Evans' claim 5 composition" is also contradicted by Evans' examples, which would have led the POSA to NaCl concentrations well below 250 mM. Petition, 36; Davies, ¶¶87-96. For example, Evans' exemplary formulations A105 and A104 differ only by their NaCl concentrations (150 mM NaCl in A104, 75 mM NaCl in A105) and the presence of 5% sucrose in A105 versus no sucrose in A104, as shown in the Table below.

Example	**Description**

A104	5mM Tris, 150 mM NaC1, 1 mM $MgCl_2$, 0.005% PS-80, pH 8.0
A105	5 mM Tris, 75 mM NaC1, 5% sucrose (w/v), 1 mM $MgCl_2$, 0.005% PS-80, pH 8.0

Evans, 22:1-2. Yet, these small differences in formulation resulted in vast differences in stability (Evans, FIG. 2) and infectivity (Evans, FIG. 3) after freeze-thaw cycles. Evans 24:18-25:24 (Example 2). Figure 2 shows that the formulation with the higher NaCl concentration, A104, lost a significant amount of material after a single freeze-thaw cycle, whereas A105 lost much less.

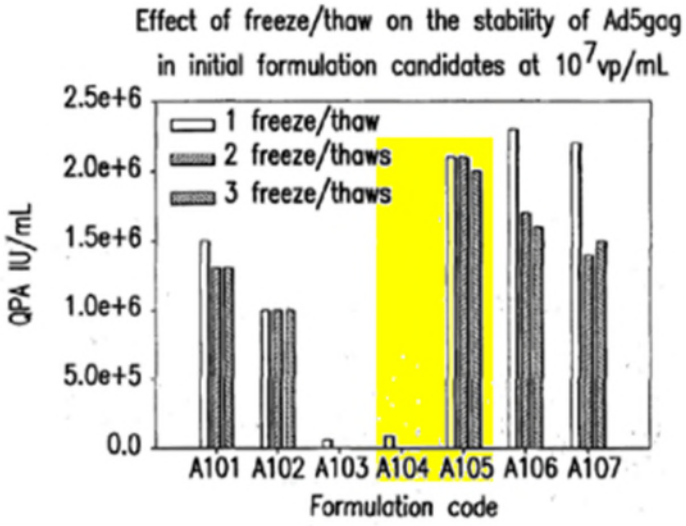


FIG.2

Figure 3 demonstrates that A105 also maintained much better infectivity than A104 after one freeze/thaw cycle. Thus, Evans' Example 2 indicates that a ***lower NaCl concentration*** was better for ensuring viral particle stability.

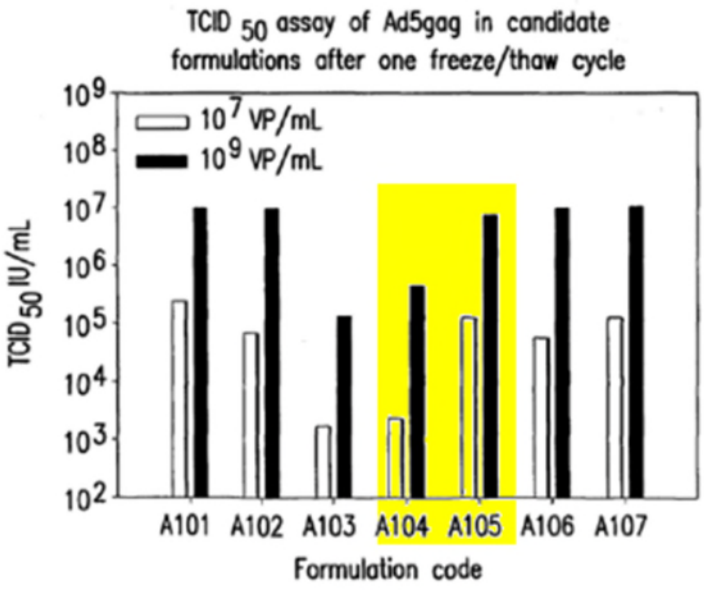


FIG.3

In the short-term stability study of Example 3, Evans compares the stability of Ad5gag in A102, A105, A106, and A107, at 10^7 and 10^9 vp/mL. *Id.*, 25:27-26:17. Shown below, A102 has the highest NaCl concentration (150 mM) of the tested formulations, whereas A105 has a lower NaCl concentration (75 mM), and A106 and A107 do not contain NaCl.

Example	Description
A102	6mM phosphate, 150 mM NaC1, 10% glycerol (v/v), pH 7.2
A105	5 mM Tris, 75 mM NaC1, 5% sucrose (w/v), 1 mM $MgCl_2$, 0.005% PS-80, pH 8.0
A106	5 mM Tris, 14% sucrose (w/v), 1 mM $MgCl_2$, 0.005% PS-80, pH 8.0
A107	5 mM Tris, 8% sorbitol (w/v), 1 mM $MgCl_2$, 0.005% PS-80, pH 8.0

Figure 6 of Evans shows that of these formulations, A102, with the ***highest NaCl concentration***, ***lost significantly more infectivity*** in 72 hours than A105, A106, and A107, as shown below with A102's results highlighted. *Id.* 26:3-17.

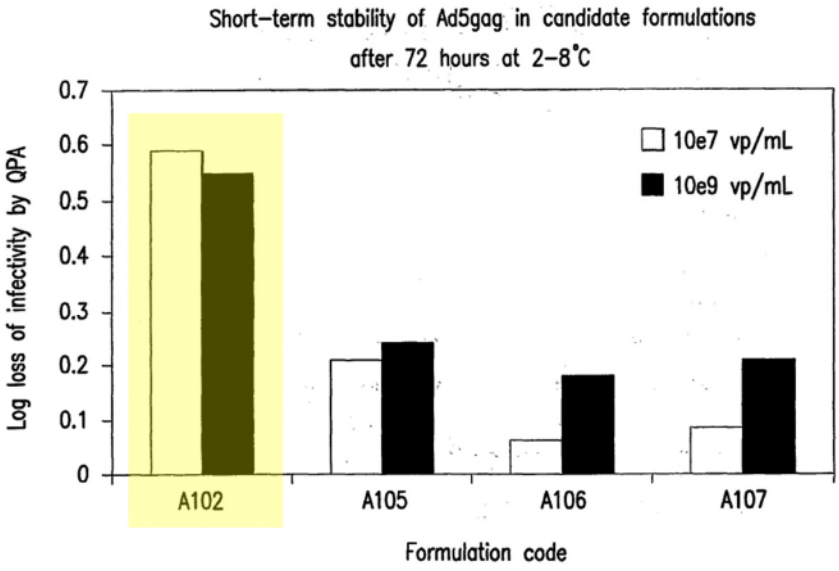


FIG.6

Example 10, which measured accelerated and real-time stability, confirmed that formulations with higher NaCl concentrations, A102-A104 (each containing 150 mM NaCl), were less stable than A105, which contained a lower concentration of NaCl (75 mM NaCl). *Id.*, 30:17-25. Example 13, a long-term stability study, tested formulations A105, A113, A114, and A116-A121 (*id.*, 33:5-34:6), but no tested formulations contained more than 75 mM NaCl (*id.*, 22:2-25).

Evans' testing results also contradict Novartis's statement that the POSA would have selected the "high end" $MgCl_2$ concentration of 5 mM. Evans' Example 5 shows that vector stability was maximized at 2 mM $MgCl_2$, whereas

increasing the quantity of $MgCl_2$ to 5 mM led to poorer stability after two months storage than 1 or 2 mM $MgCl_2$. *Id.*, 28:1-11 (Example 5); Fig. 16.

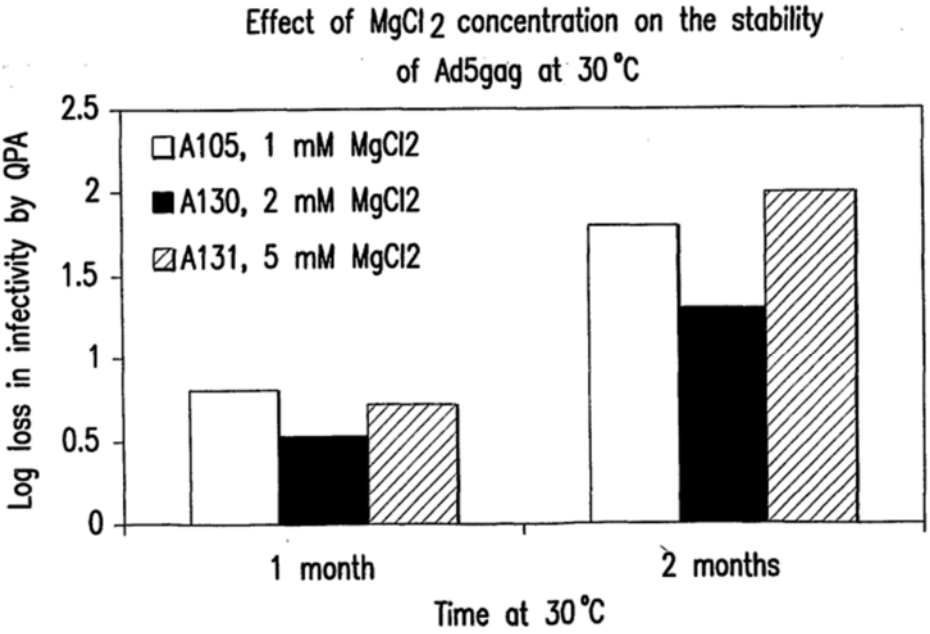


FIG.16

Novartis impermissibly "pick[s] and choose[s] from [Evans] only so much of [Evans] as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965); *see also Henny Penny*, 938 F.3d at 1332; *W.L. Gore*, 721 F.2d at 1551. Evans directs the POSA to NaCl and $MgCl_2$ concentrations far below Novartis's proposed 250 mM NaCl and 5 mM $MgCl_2$ concentrations.

iii. Novartis's Motivation Theory Relies on Hindsight

Novartis fails to prove obviousness by "not explain[ing] why a POSA would be motivated" to make a composition for "human parenteral use" (Petition, 25, 31, 33) with the claimed rAAV concentration and ionic strength, "when doing so would necessarily involve altering the inventive concept" of the '542 patent. *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1376 (Fed. Cir. 2021), *cert. denied*, 142 S. Ct. 1418 (2022).

Dr. Amiji's declaration explains why the POSA would have avoided a high salt concentration of 250 mM NaCl for human parenteral administration. Dr. Amiji emphasizes the importance of isotonic compositions for injection to avoid tissue damage and pain. Amiji, ¶¶65, 131; *see also* Davies, ¶¶97-100; Ex. 1001, 3:29-33; Ex. 1020, 615). Indeed, "[f]or an isotonic product, often it is ***advantageous to keep the concentration of salt as low as possible***." Ex. 1018, 187. Novartis, however, argues for making a composition having an NaCl concentration of 250 mM, greatly exceeding this isotonic threshold. Petition, 35-37; Davies, ¶¶101-103. This contradiction exposes that Novartis's case for obviousness "is only straightforward in hindsight." *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1355. (Fed. Cir. 2013).

"Recognizing the difficulty of casting one's mind back to the state of technology at the time the invention was made, courts have long recognized the

usefulness of evidence of the contemporaneous attitude toward the asserted invention." *Interconnect Plan. Corp. v. Feil,* 774 F.2d 1132, 1143 (Fed. Cir. 1985). Dr. Amiji explains that for viral formulations "[i]t was well known ***as of June 2004*** that it is preferrable to ***maintain the osmolarity*** of a pharmaceutical composition to be ***as close to isotonic as possible, especially for parenteral administration***, to reduce injection pain." Amiji, ¶65 (citing Ex.1008, 410-411; Ex.1021, 1525 ("Solutions to be administered subcutaneously ***require strict attention to tonicity*** adjustment.")).

Dr. Amiji also highlights Gatlin (Ex. 1008), which "***emphasizes*** *'the two formulation parameters, pH and* ***tonicity***, that are usually associated with tissue damage and injection pain,' and 'provides a parenteral product development outline' that includes guidance on ways in which pH and tonicity 'may be modified to minimize tissue damage and pain caused by a parenteral product.'" Amiji, ¶131 (citing Ex. 1008, 401-402); Davies, ¶¶36-37 (citing Ex. 1008 and Ex. 1018).

Dr. Amiji further explains that "Evans taught that its virus formulations" should "also mak[e] the formulation useful for parenteral, and especially intramuscular, injection." Amiji, ¶65 (quoting Evans, 10:18-21). Thus, Dr. Amiji's testimony and corroborating references emphasize that injectable formulations should be isotonic, particularly for "intramuscular delivery," which is

Evans' "especially preferred method" of delivery. Evans, 20:17-18; Davies, ¶¶100-103.

Serum osmolarity is about 300 mOsm. Ex. 1020, 615. "Physiological solutions with an osmotic pressure lower than that of body fluids, or of 0.9% [~150 mM] sodium chloride solution, are referred to commonly, as being hypotonic. Physiological solutions having a greater osmotic pressure are termed hypertonic." *Id*., 613; *see also* Ex. 1001, 5:15-16. A 300 mOsm NaCl solution is isosmotic with 300 mOsm serum, and thus isotonic. Novartis's proposed solution from Evans of 250 mM NaCl and 5 mM $MgCl_2$ would have an osmolarity of 515 mOsm (500 mOsm from NaCl and 15 mOsm from $MgCl_2$), which is much higher than 300 mOsm serum, and is therefore hypertonic. Davies, ¶¶101-102; Ex. 1020, 615.

Neither Novartis nor Dr. Amiji explain why the POSA would have violated the principle of "maintain[ing] the osmolarity of a pharmaceutical composition to be as close to isotonic as possible, especially for parenteral administration" (Amiji, ¶65) when the hypertonic composition they proposed would be likely to cause "tissue damage and injection pain." Amiji, ¶131.

In contrast to Novartis's argument that the POSA would have made Evans' compositions with high concentrations of NaCl, the '542 patent applied certain multivalent ions to increase ionic strength while maintaining the isotonicity of high concentration rAAV compositions. *Trivascular*, 812 F.3d at 1068 (increasing the

NaCl concentration too high "would destroy [Evans'] basic objective of" providing stable compositions for intramuscular injection.); *Chemours*, 4 F.4th at 1376. Novartis fails to point to any teaching or suggestion directing the POSA to increase the ionic strength of Evans' compositions using multivalent ions to maintain isotonicity. Thus, Novartis only reaches the claimed multivalent ion and ionic strength claim elements using impermissible hindsight.

iv. The Prior Art as Whole Undermines Novartis's Motivation Arguments

Novartis alleges that "the '542 patent admits that AAV2 vectors require elevated concentrations of salt to prevent aggregation" and that it was "known that high salt concentrations increase AAV2 vector solubility." Petition, 36 (citing Ex. 1001, 1:54-55; *see also* 4:67-5:2). Novartis ignores that the '542 patent's next sentence states "[h]owever, optimal formulations for pre-clinical and clinical studies ***should be close to isotonic*** (280-400 mOsm), especially for *in vivo* administration of vector to sites where dilution of hypertonic solutions may be slow." Ex. 1001, 5:4-7. The 515 mOsm composition proposed by Novartis (Petition, 35-36) is well above 400 mOsm. *Supra* §IV.A.2.b.iii.

Moreover, the '542 patent's statement regarding high salt concentrations cites to the purification methods of Xie et al. (Ex. 2006). Ex. 1001, 1:52-55 ("Xie and coworkers similarly reported that at concentrations exceeding 0.1 mg/mL [$1.602x10^{13}$ vg/ml], AAV2 vectors require elevated concentrations of salt to

prevent aggregation");[5] Davies, ¶¶104-105. Xie explained stated that "[h]igh concentrations of AAV-2 in the ~3.3 M CsCl from ultracentrifugal purification remained mostly in solution at 4ºC, although there was some precipitation and adhesion to glass- and plastic-ware with time…." Ex. 2006, 22-23. Thus, even for *molar* salt solutions of CsCl having osmolarity of ~ 6600 mOsm that would be unsuitable as a parenteral formulation, AAV particle precipitation was observed. Davies, ¶¶106-107. Xie further stated that a solution of "0.25 M NaCl [250 mM] resulted in ***significant loss***" of AAV. Ex. 2006, 22-23. Thus, Xie teaches that a salt concentration of 250 mM NaCl, the NaCl concentration that Novartis advocates for (Petition, 35), was inadequate to prevent significant rAAV aggregation in Xie's solution. Davies, ¶¶107-108.

Novartis also disregards that its Ground 3 reference, Frei, states its compositions "must take into account the additional ***threat to stability posed by the high salt concentrations***." Frei, 19:9-14; *see also id.*, 18:19-24; 21:25-26; 21:42-

[5] An AAV-2 concentration of 0.1 mg/ml corresponds to approximately $1.6x10^{13}$ vg/ml. rAAV genome particles have an average molecular weight of $3.746x10^{3}$ kDa, and 0.1mg/ml is $6.022x10^{16}$ kDa/ml, so a concentration of 0.1 mg/ml of rAAV particles is equal to about $1.602x10^{13}$ vg/ml. The '542 patent also notes that 0.06 mg/ml corresponds to approximately 10^{13} vg/ml. Ex. 1001, 1:58-60.

22:6; *Infra* § IV.C.2.b. In an obviousness analysis, "[e]vidence that supports, rather than negates, patentability must be fairly considered," as the POSA has "knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Fairly considering such evidence, Novartis has failed to establish a motivation to make the claimed composition.

3. Novartis Fails to Establish a Reasonable Expectation of Success

Novartis argues a "POSA would have reasonably expected Evans's claim 5 composition to prevent aggregation." *See, e.g.*, Petition, 38. Novartis's arguments fail to establish a reasonable expectation of success for at least three reasons.

a. Novartis Fails to Consider the Unpredictability of Liquid Biological Formulations

Novartis relies on what it alleges are similarities between viral vector and protein formulations. Petition, 8, 11. Dr. Amiji cites Carpenter (Ex. 1018), which states that "[i]t can be assumed that ***most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed***." Ex. 1018, 188. Considering Novartis's own cited references, including Huang, Croyle (Ex. 1013), and Wright (Ex. 1007), the POSA would have been skeptical that a high-concentration rAAV aqueous composition would have been feasible. *Supra* §IV.A.2.a.

Novartis argues that "distinctions between adenovirus and AAV lack meaningful differences with respect to 'proper conditions to prevent aggregation'" and "a POSA … would have reasonably expected Evans's compositions to provide similar, if not better stability for storing AAV particles." Petition, 29. Novartis's argument fails because what might work for one type of viral vector (*e.g.*, an adenovirus), does not predict what will work for another (*e.g.*, rAAV). Davies, ¶¶109-110. Carpenter explains that "[e]very protein and product has unique characteristics, some of which may cause difficulty in designing stable formulations." Ex. 1018, 118. Evans further demonstrated that even for a single viral vector, minor changes in excipients can produce dramatic changes in stability. *Supra* §IV.A.2.b.ii (citing Evans 24:18-25:24 (Example 2), FIGS. 2, 3) (comparing stabilities of formulations A104 and A105); Davies, ¶¶111-112.

The Board should find here, as it has before, that a reasonable expectation of success argument that fails to deal with this unpredictability cannot prove obviousness. *Amneal Pharms. LLC v. Cubist Pharms. LLC*, IPR2020-00193, Paper 7 at 32-22 (PTAB May 29, 2020); *Sandoz Inc. v. AbbVie Biotechnology Ltd. et al.*, IPR2017-01823, Paper 16 at 14 (PTAB Feb. 9, 2018); *Coherus Biosciences Inc. v. AbbVie Biotechnology Ltd.*, IPR2016-01018, Paper 14 at 4 (PTAB Feb. 2, 2017); *Momenta Pharms., Inc. et al. v. Bristol-Myers Squibb Co.*, IPR2015-01537, Paper 37 at 12-13 (PTAB Dec. 22, 2016).

b. Evans Does Not Support a Reasonable Expectation of Success

Novartis alleges that "Evans teaches that its compositions 'show enhanced stability for longer periods of time at temperatures in the range of 2-8°C,' 'allowing for storage and eventual host administration of these liquid formulations over about a 1-2 year period.'" Petition, 39-40 (quoting Evans, 2:29-32, 4:21-25). Evans, however, does not contain any disclosure relating to particle aggregation.

Evans only conducted stability testing on formulations having viral particle concentrations ranging from 10^7 vp/mL to 10^{11} vp/ml, which is several orders of magnitude below the 10^{13} vp/ml upper limit of Evans' concentration range. *Supra* §IV.A.2.b.ii (citing Evans, 24:21-22 and 25:14-15 (Example 2), 25:31-32 and 26:3-4 (Example 3), 29:6 (Example 7)); Davies, ¶¶113-114.

None of the exemplary formulations in Evans have a concentration greater than 150 mM NaCl, and the most stable formulations contained 75 mM or less NaCl, with ionic strengths below 200 mM. *Supra* §IV.A.2.b.ii. Evans did not address viral particle aggregation, instead focusing on the impact of cryoprotectants, radical scavengers, and/or chelators to address stability issues caused by radical oxidation. Evans, 3:19-4:2. Evans nonetheless demonstrated that small changes to excipients can dramatically change the stability of a viral vector composition. *Id.* (citing Evans 24:18-25:24 (Example 2), FIGS. 2, 3); Davies, ¶115.

Novartis fails to point to any disclosure in Evans that would have supplied the POSA with a reasonable expectation that compositions comprising rAAV at a concentration $>10^{13}$ vg/ml and an ionic strength greater than 200 mM would not result in significant aggregation. *Infra* § IV.A.4.

c. Huang, Mingozzi, and Other Cited Art Do Not Remedy Novartis's Failure to Establish a Reasonable Expectation of Success

As a "touchstone of obviousness," a reasonable expectation of success requires not only an "expectation that prior art elements are capable of being physically combined, but also that the combination would have ***worked for its intended purpose***." *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009). Novartis's statement that "based on Huang, the POSA would have reasonably expected that high-concentration AAV compositions (e.g., 5-10x10^{13}vg/ml) could be achieved and utilized for successful gene transfer" (Petition, 32) is contradicted by Huang's finding that high-concentration compositions exhibited "***gene transfer efficiency [that] was 10-100 folds lower"*** than lower concentration rAAV compositions. Huang, S286; *supra* §IV.A.2.a; Davies, ¶¶116-117.

Novartis's statement that Mingozzi supports its argument is similarly unfounded. Petition, 32-33 (citing Mingozzi, 10497-98). Neither Novartis nor Dr. Amiji provide any information regarding the formulation of Mingozzi's

composition, whether it contained aggregates or was even stored before administration. Davies, ¶¶118.

Novartis argues that "compositions capable of storing purified AAV vector particles at the claimed concentrations 'without significant aggregation' were described in Wright [Ex. 1007] and, therefore, cannot form the basis for patentability." Petition, 39-40. But Wright does not provide any information about the composition, including its pH, ionic strength, and whether there were multivalent ions present. Ex. 1007, 175 (stating that the formulations are based on "unpublished data"); *supra* §IV.A.2.a; Davies, ¶¶119-120; *KSR*, 550 U.S. at 418; *W.L. Gore*, 721 F.2d at 1548 ("Each claimed invention must be considered as a whole.").

Novartis argues that "the prior art taught numerous instances of high ionic strength virus storage compositions." Petition, 37. The Petition cites as evidence Liu (Ex. 1009) and Potter (Ex. 1011). Petition, 37 (citing Ex. 1009 [00366], [00369], Table 15; Ex.1011, 417-419, 429). But Novartis ignores that the cited formulations in both Liu and Potter, like Evans' examples, contain virus particle concentrations several orders of magnitude below the claimed concentration exceeding 10^{13} vg/ml. According to Dr. Amiji, Liu's Table 15 ml (Ex. 1009, [00370]) contained a concentration of only "$3.24x10^{8}$ (viral particles) vp/ml" (Amiji, ¶285) which is several orders of magnitude below the claimed rAAV

concentration exceeding 10^{13}. Dr. Amiji states that "Potter reported yields of 1.2-4.2x10^{12} total infectious particles," also well below the claimed rAAV concentration. Amiji, ¶139 (Ex. 1011, 413-14, 419). Given the POSA's knowledge that aggregation increases with rAAV concentration (*supra* §IV.A.2.a), Novartis fails to explain how Liu and Potter would have supported a reasonable expectation of success for claims 5 and 6. Davies, ¶¶121-124.

Novartis alleges that Evans renders obvious the claimed concentration and ionic strength elements. Petition 33, 37 (citing *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1368 (Fed. Cir. 2012)). For reasonable expectation of success, however, the Board should consider the claim as a whole, including elements in claims 5 and 6 that relate to the detection of aggregates. *Ruiz*, 357 F.3d at 1275 (Fed. Cir. 2004). "*Alcon Research* does not stand for the proposition [Novartis] would have it support, namely, that compositions comprising multiple components with amounts of each component falling within the recited ranges necessarily meets the functional limitations." *Spectrum Solutions LLC v. Diagnostics*, IPR2021-00851, Paper 13 at 16-17 (P.T.A.B. Nov. 18, 2021). As in *Spectrum*, "[Novartis] provides no cogent argument for extending *Alcon Research* to stand for the proposition that all compositions meeting the recited ranges of multiple components" also meet the lack of aggregate standards of claims 5 and 6. *Id.* at 17; *Infra* § IV.A.4.

4. Novartis Fails to Establish that the Claims 5 and 6 Are Obvious

Both claim 5 and claim 6 relate to specific measures setting quantitative limits on aggregate formation. Davies, ¶¶125-126, 130-134. Novartis, however, fails to provide any evidence that the particle size elements recited in claims 5 and 6 necessarily flow from the combination of elements Novartis has alleged was obvious. Petition, 40-42 (claims 1 and 5), 44 (claim 6). To meet the standard for inherency in the context of obviousness "[a] party must … meet a high standard … [that] the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *PAR Pharm*, 773 F.3d at 1196. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id*. Novartis bears the burden in establishing inherent obviousness. *Knauf Insulation, Inc. v. Rockwool Int'l A/S*, 788 F. App'x 728, 734–35 (Fed. Cir. 2019) ("it was not Patent Owner's burden to establish that the inherent result" was not inherent, "it was Petitioner's burden to prove that every limitation in the claim was found in the prior art, either inherently or explicitly."). Novartis failed to meet its burden.

a. Claims 5 and 6 Carry Patentable Weight

Without evidence to support its inherent obviousness argument of claims 5 and 6, Novartis distorts the prosecution history and litigation record. Novartis

wrongly argues that "Patent Owners admit that claim 5 merely "provide[s] [a] method[] of ensuring that there is no substantial aggregation." Petition 41 (citing Ex. 1023, 72; Ex.1025, ¶¶194-195). Claims 5 and 6, however, "provide[] the criteria by which the" composition for the storage of purified rAAV vector particles "is analyzed" (Davies, ¶¶125-128, 129-134). *In re Jasinski*, 508 F. App'x 950, 952 (Fed. Cir. 2013); *see also Vizio, Inc. v. Int'l Trade Comm'n*, 605 F.3d 1330, 1340 (Fed. Cir. 2010) (holding that claim language going to "the essence or a fundamental characteristic of the claimed invention" was "properly construed as a limitation.").

For claim 5, the '542 patent explains that "Rh values >20 nm are deemed to indicate the occurrence of some level of aggregation." Ex. 1001, 9:25-27. By analyzing average particle radius, the inventors determined that ionic strength was a key determinant of rAAV. *Supra* §II.A.

For claim 6, the '542 patent explains that the presence of aggregates can be measured through vector recovery following filtration through a 0.22 µM filter. Ex. 1001, 8:19-44. These filtration experiments allowed for the comparison of aggregate formation for the formulations CF, TF1, and TF2 having different vector concentrations. *Supra* §II.A

Claims 5 and 6 carry patentable weight, because they relate to the quantification of rAAV aggregation (or the absence of aggregates) more accurately

than other methods of detection, including visual inspection and analytical methods such as A_{320}/A_{260} absorbance (*infra* § IV.C.4). Davies, ¶¶46-51 (citing Ex. 2009). Thus, claims 5 and 6 each relate to "a fundamental characteristic of the claimed invention" that should be "properly construed as a limitation" for determining whether a composition is within the scope of the claims. *Vizio*, 605 F.3d at 1340.

b. Genzyme Did Not Acquiesce to the Unpatentability of the Limitations in Claims 5 and 6

Novartis erroneously argues that Genzyme acquiesced to the Examiner's statement "[s]ince, all the components … are the same as disclosed in the cited prior art, these features will necessarily follow from the composition disclosed in the art." Ex. 1002, 86. Genzyme never acquiesced to the Examiner's incorrect inherency arguments. In fact, as Novartis acknowledges, Genzyme disputed the Examiner's rejection. Petition, 42 n.6.

The Federal Circuit in *TorPharm, Inc. v. Ranbaxy Pharms., Inc.* rejected Novartis's proposition that "Patent Owner's silence constitutes a binding admission" (Petition, 42), holding instead that a "patentee is not required to fight tooth and nail every possibly adverse thought an examiner commits to paper, nor to advance redundant arguments for patentability." 336 F.3d 1322, 1330 (Fed. Cir. 2003); *see also Woods v. DeAngelo Marine Exhaust, Inc.*, 692 F.3d 1272, 1287 (Fed. Cir. 2012) ("A patent applicant is not presumed to have conceded the presence in the prior art of every claim limitation he had no reason to dispute").

"[A]cquiescence may be found where the patentee narrows his or her claims by amendment," which may be relevant for claim interpretation. *TorPharm*, 336 F.3d at 1330. "But these principles do not suggest that a patentee may advance during litigation only those arguments in support of patentability that were made before the Patent Office." *Id.* Novartis adduces no evidence suggesting that Genzyme acquiesced that the elements of claims 5 and 6 were in the prior art, and thus the Board should reject its argument.

c. Novartis Fails to Establish that Claim 5 Is Inherently Obvious

Novartis alleges that "[b]ecause Evans's claim 5 composition prevented aggregation, a POSA would have reasonably expected AAV particles stored therein would have an Rh of <~20 nm measured by DLS." Petition, 42. Novartis points to no evidence showing that Evans even mentioned aggregation, much less "recombinant AAV vector particles hav[ing] an average particle radius (Rh) of less than about 20 nm."

Novartis alleges that a "POSA would have reasonably expected success in minimizing particle size in view of Huang's teaching that its optimized compositions 'could lead to a 30-50% reduction in the size of aggregates at high vector concentrations.'" Petition 43 (citing Huang, S286). The POSA would have recognized that Huang's composition still contained aggregates and that Huang

provided no information about its formulation or what the purported size reduction represents. *Supra* §IV.A.2.a.

Liu's statement that adenovirus compositions showing "no signs of settling or precipitation" is similarly irrelevant to claim 5's radius requirement. Petition, 43; *supra* §IV.A.3.c. Liu's visual methods would be understood to be far less sensitive than DLS. Visible particles are magnitudes larger than rAAV particles, so eliminating or preventing visible particles does not mean that subvisible aggregates are not present. Davies, ¶127.

Novartis bears the burden in establishing inherent obviousness for claim 5. *Knauf Insulation*, 788 F. App'x at 734–35. Novartis, however, ***fails*** to adduce any evidence that for the claimed composition "the purified, recombinant AAV vector particles" would necessarily and inevitably have had "an average particle radius (Rh) of less than about 20 nm as measured by [DLS]." For claim 5, Novartis cannot possibly meet the standard for inherency in the context of obviousness. *PAR Pharm.*, 773 F.3d at 1196.

d. Novartis Fails to Establish that Claim 6 Is Inherently Obvious

Novartis argues that "[t]he '542 patent does not identify anything critical about the recited recovery rate" and argues that claim 6 is an inherent feature of the prior art. Petition, 44. The claimed percent recovery following filtration through a 0.22 μm filter, however, is a measure of the degree of aggregation within the

composition (Davies, ¶¶130-134), which goes to a "fundamental characteristic of the claimed invention." *Vizio*, 605 F.3d at 1340.

When the inventors assessed the effect of ionic strength on aggregation by measuring vector recovery after filtration through a 0.22 μm filter they found compositions having ionic strength greater than 200 mM surprisingly resulted in recoveries ***exceeding 90%***, whereas compositions having ionic strengths below 200 mM resulted in recoveries below 80%. Ex. 1001, 8:19-44. The '542 patent explains that "[w]ithin the variability of the assays used, vector was recovered fully at both target concentrations using TF2, ***indicating that aggregation was prevented***." Ex. 1001, 8:44-46; Davies ¶¶131 (citing Ex. 2009). It was known that rAAV aggregates in compositions could lead to, *e.g.*, loss of infectivity and adverse immune responses, and the POSA understood minimizing aggregation is critical. Ex. 1001, 1:15-39.

Novartis bears the burden in establishing inherent obviousness for claim 6 but provides no evidence of inherency. *Knauf Insulation*, 788 F. App'x at 734–35. Thus, Novartis cannot possibly meet the high standard for inherency. *PAR Pharm.*, 773 F.3d at 1196.

B. Discretionary Denial of Ground 1 Under § 325(d) Is Warranted

Under the Board's two-part framework set forth in *Advanced Bionics, LLC v. Med-El Electromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7

(PTAB Feb. 13, 2020) (precedential) ("*Advanced Bionics*"), discretionary denial of Ground 1 under § 325(d) is warranted.

1. The Examiner Considered Evans and Huang, and Mingozzi is Cumulative

Part one of the *Advanced Bionics* framework relates to whether the same or substantially the same art or arguments were presented previously to the Office. *Advanced Bionics*, 10. Novartis concedes that the Examiner considered "U.S. Publication No. 2004/0166122 ("Evans 2" (Ex.1027)), which is ***essentially identical*** to Evans." Petition, 62 n.9. Huang was cited in an Information Disclosure Statement considered by the Examiner and described in detail in the '542 patent's background section. Ex. 1002, 99 (showing Huang as "considered"); Ex. 1001, 1:41-51, 2:44-47. Thus, with respect to Evans and Huang, "the same or substantially the same art [was] previously presented to the Office." *Advanced Bionics*, 10.

Although Mingozzi was not cited during prosecution, its disclosure is cumulative to other art of record, including Huang. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17 (Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) ("*Becton, Dickinson*") (The Board's § 325(d), evaluation should consider "the cumulative nature of the asserted art and the prior art evaluated during examination"). Novartis relies on Mingozzi to supply the rAAV vector concentration exceeding 10^{13} vg/ml. Petition, 25, 31, 32-33. During

prosecution, the Examiner relied on Zolotukhin (Ex. 1026) to provide the concentration element (Ex. 1002, 316-17), so the "Examiner identified and summarized other references having that [concentration] feature" in the Examiner's view. *Darfon Elecs. Corp. v. Michael Shipman*, IPR2022-01008, Paper 11 at 13 (PTAB Dec. 2, 2022).

Additionally, Novartis relies on both Huang and Mingozzi to provide high-titer AAV compositions of concentrations over 10^{13} vg/ml. Petition, 25 (citing Mingozzi, 10497), 32-33 (citing Huang, S286).

Novartis argues that "Mingozzi achieved successful gene delivery *in vivo* with its high-titer AAV compositions," which "can[not] be found in the references cited during prosecution." Petition, 63. The distinction based on Mingozzi's alleged "successful gene therapy" does not render Mingozzi substantially different than Huang with respect vector concentration. Thus, "[Novartis] has not indicated, in the context of 35 U.S.C. § 325(d), any material differences between [Mingozzi] and [Huang]. Indeed, [Novartis] relies upon them in the alternative for its obviousness challenge." *Bio-Rad Labs., Inc. v. 10X Genomics, Inc.*, No. IPR2019-00566, Paper 21 at 7 (PTAB Jul. 22, 2019).

2. Novartis Fails to Identify a Material Error in Examination

Part two of *Advanced Bionics* considers "whether the Petitioner has demonstrated that the Office erred in a manner material to the patentability of [the]

challenged claims." *Advanced Bionics*, 8. *Becton Dickenson* factors (c), (e), and (f) relate to whether the Petitioner has demonstrated a material error by the Office." *Advanced Bionics*, 10. Novartis has not demonstrated a material error.

Novartis's argument that "the Examiner did not substantively evaluate any of Petitioners' asserted art" (Petition, 64 citing factor (c)) is disproven by the prosecution history that repeatedly characterized Evans as "pertinent art." Ex. 1002, 191, 224, 321. The Examiner's characterization of Evans 2 as "pertinent art" indicates that Evans 2 "was evaluated during prosecution, even though no rejection rested on that reference." *Sonos, Inc. v. Google LLC f/k/a Google Inc.*, IPR2022-01592, Paper 9 at 26 (PTAB Apr. 14, 2023). Moreover, the Examiner identified disclosure within Evans 2 that Novartis has also attempted to correlate to elements recited in claim 1. The Examiner stated Evans 2 "disclose[s] stable viral vector formulations for gene therapy and other clinical applications generally comprising up to about lx10^{13} viral particles/ml in a suitable buffer … pH 7.5, 250 mM NaCl … $MgCl_2$ in the range of 0.l mM to about 10 mM." Ex. 1002, 321 (citing Evans 2, ¶¶ [0051], [0056], [0060], [0079], "entire disclosure at pages 5-6 … and claims"). Novartis relies on similar disclosures in Evans for claim 1's rAAV vector concentration (Petition, 30), pH buffer (*id.*, 33-34), multivalent ion, (*id.*, 34-35) and ionic strength (*id.*, 35-36) elements.

Novartis also argues that "[f]actor (e) also supports institution in view [of] the Examiner's mistakes" of ignoring "Huang's highly-relevant teachings that common formulation techniques can be used to reduce aggregation in high-titer rAAV compositions, and Wright's teachings that render the challenged claims obvious." Petition, 65. The Examiner neither misapprehended nor overlooked Huang or Wright.

Novartis admits that Huang failed to curtail AAV aggregation at concentrations exceeding 10^{13} vg/ml. Petition, 19 (citing Huang, S286); *supra* §IV.A.2.a. Novartis, however, fails to identify what "highly-relevant teachings" the Examiner misapprehended or overlooked in Huang's one-paragraph abstract.

Wright, which Novartis does not rely on as part of Grounds 1 or 3, states that the "mechanism of vector aggregation is ***not well understood***" (Ex. 1007, 175) and that the "nature of the interparticle interactions that result in aggregation ***has not been well characterized***" (*id.*, 176). Wright discloses nothing about the composition's vector genome concentration (vg/ml), pH, ionic strength, and excipients, or whether it was suitable for human clinical use. *Id.*, 175. Thus, the Examiner likely did not reference Huang or Wright, because neither would have supported an obviousness rejection.

Novartis accuses the Examiner of "fail[ing] to realize Evans 2 is 35 U.S.C. §102(e) *prior* art, and mistakenly exclud[ing] that reference from his obviousness

rejections." Petition, 65. Novartis asks the Board to believe that an experienced Examiner who identified Evans as "pertinent art" in three instances failed to observe Evans 2's cover which states its March 2, 2004 filing date, or Evans 2's claims of priority to a non-provisional and a provisional application, both filed years before the '542 patent's priority date. Novartis's only "proof" of its theory is semantic speculation that the Examiner characterizes Evans 2 as "pertinent art" rather than "pertinent *prior* art" (Petition, 65-66).

Likewise, the Examiner was ***not*** "led astray by Patent Owner's allegation that 'causes of aggregation of recombinant AAV particles' were unknown before the '542 patent." Petition, 66 (citing Ex.1002, 242). Novartis points to "§ IV.C" of its Petition to argue that "variables to reduce rAAV aggregation … were also well known and already used to minimize rAAV aggregation." *Id.* The references relied on in "§ IV.C," including Huang and Wright belie Novartis's argument. Huang provided no detail on how to reduce aggregate particle sizes. *Supra* §IV.A.2.a

For *Becton Dickinson* factor (f), Novartis does not identify anything specific in the Petition or Dr. Amiji's declaration that would "outweigh Petitioner's failure in this proceeding to show material error in the Examiner's consideration." *Biocon Pharma Ltd. v. Novartis Pharms. Corp.*, IPR2020-01263, Paper 12 at 18 (PTAB Feb. 16, 2021). Thus, factor (f) fails to support institution.

The Ground 1 art is the same or substantially the same art that was previously presented to the Office and Novartis has not demonstrated that the Examiner erred when considering the prior art. The Board should deny Ground 1 under § 325(d).

C. Ground 3: The Petition's Combination of Frei, Huang, and Mingozzi Fails to Render Claims 5 and 6 Obvious

Novartis fails to establish that Ground 3 renders obvious at least three elements of claims 5 and 6: (1) the rAAV "concentration exceeding $1x10^{13}$vg/ml up to $6.4x10^{13}$ vg/ml"; (2) "the ionic strength of the composition is greater than 200 mM"; and (3) the respective particle size limitations of claims 5 and 6.

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Novartis fails to establish why the POSA would have gone from Frei, which contains no indication that increased ionic strength suppresses particle aggregation, but rather focuses on enhancing stability through the addition of polyhydroxy hydrocarbons (Frei, 19:17-20), to the compositions of claims 5 and 6 with a reasonable expectation of success. In addition, Novartis fails to provide any evidence that the particle size and product recovery elements of claims 5 and 6, respectively, would inherently have resulted from the claimed compositions.

1. Frei Does Not Disclose a Composition Having the Claimed Viral Genome Concentration

Novartis fails to provide substantive evidence that supports its contention that Frei discloses a composition comprising viral particles at "a concentration exceeding $1x10^{13}$ vg/ml up to $6.4x10^{13}$ vg/ml." Petition, 52. The Petition cites Frei's D-1 composition, which "has a virus concentration of '$1.6x10^{13}$ particles/ml'" and contends "[p]rovided that >62.5% of the particles contain vector genomes, Frei's D-1 composition comprises viral vector particles exceeding $1x10^{13}$vg/ml." Petition, 52 (citing Ex.1004, 22:31; Ex.1025, ¶¶ 223-224).

Novartis provides no basis for why the POSA would have made that assumption. Davies, ¶¶135-138. Novartis only cites Dr. Amiji who "does not cite to any additional supporting evidence or provide any technical reasoning to support his statement …. and is entitled to little weight." *Xerox*, IPR2022-00624, Paper 9 at 15.

In fact, Dr. Amiji's declaration indicates that the POSA ***would not have assumed*** that Frei's viral particle compositions were substantially free of empty capsids, with Wright (Ex. 1007) teaching rAAV compositions may include as much as a ***10-fold excess in empty capsids***. Amiji, ¶119 (citing Ex. 1007, 176). Lochrie states that "***more than 80% of AAV material*** … may be empty capsids." Lochrie, 4:20-23. Frei states its compositions "can be prepared during purification of the virus in a gel filtration chromatography column." Frei, 11:5-9. However,

Lochrie states "column chromatography purification techniques ***do not separate packaged capsids from empty capsids***." Lochrie, 4:20-23; Davies, ¶137.

Novartis's supporting testimony and evidence, therefore, demonstrate that the POSA would have understood that a composition having $1.6x10^{13}$ particles/ml, would contain a far lower vector genome concentration than 10^{13} vg/ml.

2. Novartis Fails to Provide a Motivation to Combine Frei, Huang, and Mingozzi to Arrive at the Claimed Composition

a. Novartis Fails to Establish a Motivation to Develop a Composition Having the Claimed rAAV Concentration, Ionic Strength, and One or More Multivalent Ion

Novartis's argument fails to establish that the POSA would have been motivated to develop a composition comprising an rAAV "concentration exceeding $1x10^{13}$ vg/ml" with an ionic strength "greater than 200mM." Novartis cites to its Ground 1 argument based on "citing Huang, Mingozzi, Clark, Gatlin" to argue that the POSA would have administered a "concentration exceeding $1x10^{13}$ vg/ml." Petition, 49, 52. The Board, however, must "be careful not to allow hindsight reconstruction of references . . . without any explanation as to *how* or *why* the references would be combined to produce the claimed invention." *TriVascular*, 812 F.3d at 1066.

By addressing the concentration and ionic strength elements separately, Novartis ignores the inventive combination and falls prey to "hindsight syndrome" by reasoning backward from the teaching of the patent itself." *Creo Prod., Inc. v.*

Presstek, Inc., 166 F. Supp. 2d 944, 966 (D. Del. 2001), aff'd, 305 F.3d 1337 (Fed. Cir. 2002); ; *see also Rockwell Int'l*, 147 F.3d at 1364; *Jones*, 727 F.2d at 1529; *W.L. Gore*, 721 F.2d at 1548. The teachings in the relevant timeframe demonstrated that higher rAAV concentration led to increased aggregation but failed to provide guidance on how to solve the aggregation problem. *Supra* §IV.A.2.a (citing Huang, S286; Ex. 1013, 1286; Ex. 1007, 175). Novartis fails to establish motivation to make a composition having an rAAV "concentration exceeding $1x10^{13}$ vg/ml," much at an ionic strength over 200 mM.

b. Novartis Ignores Frei's Teaching that High Salt Concentrations Pose a Threat to Stability

The Petition states that "Frei taught that '[p]referably, the salt is sodium chloride present in the amount of 0.6 to 10.0 mg/ml.'" Petition, 54 (citing Frei, 5:39-6:5). To reach the claimed ionic strength, Novartis argues that the POSA would "would have been motivated to select the ***high end*** of Frei's concentration ranges, since Wright identified ionic strength as a condition that may affect vector aggregation." Petition, 55 (citing Ex.1007, 175).

Novartis omits that Frei states that its vector concentration methods "must take into account the additional ***threat to stability posed by the high salt concentrations*** in the product eluted from the anion exchange column." Frei, 19:9-14; *see also id.*, 21:25-26 (referring to the "vulnerability of the DEAE pool — with its high salt concentration); 21:42-22:6 ("the methods of the present invention

allow for greatly enhanced virus stability, despite the mechanical shear forces of concentrating the virus, and ***despite harsh conditions such as high salt levels*** in a DEAE pool.").

Novartis also omits from its quote of Frei (Petition, 54 (citing Frei, 5:39-6:5)) Frei's statement that NaCl concentration is "***more preferably*** in an amount of about 5.8 mg/ml." Frei, 6:5-6:6. Indeed, Example D-1 of Frei—the exemplary formulation relied on by Novartis (Petition, 54-55)— contains an NaCl concentration of 100 mM, which is 5.8 mg/ml. Frei, 22:24-3. In fact, none of Frei's exemplary compositions containing particle concentrations exceeding 10^{13} particles/ml contain more than 100 mM NaCl. Frei, 22:15-23:20 (Examples D1-D3, S-1); Davies, ¶¶139, 143-144.

Novartis states that "Frei itself teaches that '[i]n addition to stabilizing the composition, sodium chloride may suppress the rate and extent of the appearance of by-products of fermentation, resulting in a more pharmaceutically elegant presentation that may have reduced antigenicity potential due to protein aggregates' and '[t]he addition of sodium chloride does not affect the pH of the formulation.'" Petition, 55 (citing Ex. 1004, 6:7-11). The POSA considering the quoted passages of Frei, would not have understood these passages to support ***maximizing*** NaCl concentration to avoid aggregation, as Novartis alleges. Davies, ¶¶ 140-142.

In its section relating to the claim limitation that requires storage "without significant aggregation," the Petition states that "Frei also demonstrated stability after short- and long-term storage (1 week to 12 months" for multiple adenoviral compositions, albeit at lower virus concentrations."). Petition, 57 (citing Frei, Tables 1-5). Novartis, however, ignores that Representative Formulation Examples 1-4 do not contain any NaCl, and Example 5 contains 5.8 mg/ml NaCl, all well below the 10 mg/ml NaCl concentration level maximum disclosed by Frei. Frei, 10:5-15:5; Davies, ¶¶144-145.

By selectively choosing Frei's disclosures that help its arguments, and omitting the majority of Frei's teachings that do not, Novartis's arguments violate "the longstanding principle that the prior art must be considered for all its teachings, not selectively." *Henny Penny*, 938 F.3d at 1332; *see also W.L. Gore*, 721 F.2d at 1551; *Wesslau*, 353 F.2d at 241 (C.C.P.A. 1965). Frei's disclosure as a whole fails to support Novartis's motivation theory.

Novartis's reliance on Wright (Ex. 1007) is similarly unavailing. Petition, 55. As explained for Ground 1, the POSA would not have understood Wright to teach or suggest adjusting ionic strength by adjusting NaCl and $MgCl_2$ concentrations as Novartis proposes. *Supra* §IV.A.2.b.i; Davies, ¶146. Increasing ionic strength to prevent significant aggregation in rAAV compositions "is only

straightforward in hindsight" based on the teachings of the '542 patent. *Leo Pharm.*, 726 F.3d at 1355.

Novartis alleges that "the '542 patent admits 'AAV2 vectors require elevated concentrations of salt to prevent aggregation.'" Petition, 55 (citing Ex.1001, 1:54-55, 4:67-5:2). As explained for Ground 1, however, Novartis's reliance on this alleged "admission" falls apart when the context of the '542 patent's statement on salt concentration and the reference to which it refers, Xie (Ex. 2006), are considered. *Supra* §IV.A.2.b.iv; Ex. 2006 at 23 (Xie's rAAV composition containing "0.25 M NaCl [250 mM] resulted in ***significant loss***"); Davies, ¶147.

In an obviousness analysis, "[e]vidence that supports, rather than negates, patentability must be fairly considered," as the POSA has "knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." *In re Dow Chem. Co.*, 837 F.2d at 473. Fairly considering Xie, Novartis fails to establish a motivation to make the claimed composition based on Frei, Huan, and Mingozzi.

3. Novartis Fails to Establish a Reasonable Expectation of Success

Novartis argues that the POSA would have reasonably expected success in developing concentrated AAV compositions. Petition, 52 (quoting Frei, 7:7-8).

Novartis's arguments fail to establish a reasonable expectation of success for at least three reasons.

a. Novartis Fails to Consider the Unpredictability of Liquid Biological Formulations

Novartis repeatedly relies on what it alleges are similarities between viral vector and protein formulations. Petition, 8, 11. Dr. Amiji cites Carpenter (Ex. 1018), which states that "[i]t can be assumed that ***most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed***." Ex. 1018, 188. Thus, as explained in Ground 1, the art is unpredictable and the POSA would have been skeptical that a concentrated rAAV composition would have been feasible particularly in view of the many accounts detailing rAAV aggregation issues. *Supra* §IV.A.3.a; Davies, ¶148..

b. Novartis's Reasonable Expectation of Success Arguments Ignore Frei's Disclosure Regarding the Threat Posed by High Salt Concentration

The Petition alleges that "Frei taught that its salt-containing DEAE pool could be stored 'for >10 days at 2-10°C (thus allowing for subsequent steps of virus concentration and/or gel filtration to be performed on separate days with substantial flexibility across a 10 day period.)'" Petition, 57 (citing Frei, 22:10-12). Frei, however, taught that its compositions were stable despite "the additional ***threat to stability posed by the high salt concentrations***…." Frei, 19:9-14; *see also supra* §IV.C.2.a. Indeed, the POSA would have understood Frei's preferred

NaCl concentration range was significantly lower than the NaCl concentrations Novartis applies to meet the 200 mM ionic strength element. *Supra* §IV.C.2.b; Davies, ¶149.

c. The POSA Would Not Have Considered Frei's Light Scattering or Visual Methods to Effectively Detect Significant Aggregation

Contrary to the Petition's assertion, "Frei's light scattering data" would not have been understood by the POSA to "confirm[] its D-1 composition prevented aggregation" in its examples (Petition, 56). Davies, ¶¶50-52, 150. In contrast to the particle radius determination of claim 5 and the product recovery following filtration of claim 6 (*supra* §II.A), Frei's disclosed A_{320}/A_{260} absorbance analysis has been shown to be unable to detect the presence of significant aggregates. Davies, ¶¶46-52 (citing Ex. 2009).

Novartis alleges that a "POSA would have reasonably expected success in using the high ends of Frei's concentration ranges based on the teachings of Potter, Liu, Wright, and the admissions in the '542 patent." Petition 56; *see also id.* 57 n.8, 58. Wright does not provide any information about its composition, including its pH, ionic strength, and whether there are multivalent ions present. *Supra* §IV.A.3.c (citing Ex. 1007, 175); Davies, ¶151. Liu and Potter are similarly unavailing, because of their low viral particle concentration and the fact that visual

methods cannot accurately detect the presence of aggregates. *Supra* §IV.A.3.c; Davies, ¶151.

The Board should consider whether the claim as a whole, including elements in claims 5 and 6 that relate to the detection of aggregates in the claimed composition, is obvious. *Ruiz*, 357 F.3d at 1275 (Fed. Cir. 2004); *Spectrum*, IPR2021-00851, Paper 13 at 16-17. As explained above, Novartis fails to provide any evidence that the aggregate standards of claims 5 and 6 would have been inherently met. *Infra* §IV.A.4.

4. Novartis Fails to Establish that Frei in View of Huang and Mingozzi Render Claims 5 and 6 Obvious

Ground 3 rehashes Ground 1's arguments relating to claims 5 and 6. Petition, 59 (claim 5), 60 (claim 6). Ground 3's arguments for claims 5 and 6 fail for the same reason as Ground 1. *Supra* §IV.A.4. Ground 3 also rehashes Ground 1's arguments for "reasonably expected success in minimizing particle size in view of Huang and Liu." Petition, 60 (claim 5), Petition, 60-61 (claim 6). Novartis's reasonable expectation arguments fail for the same reason as Ground 1. *Supra* §IV.A.4.c-IV.A.4.d.

Novartis introduces an additional allegation for claim 5, which is that "Frei's light scattering data shows that its D-1 composition contained monomeric particles." Petition, 59 (citing Ex.1025, ¶¶ 258-259). Frei's compositions do not contain rAAV particles, the claimed rAAV concentration, or the ionic strength

required by claims 5 and 6 and certainly do not show that the elements of claims 5 and 6 necessarily and inevitably result from the claimed compositions. *Supra* §§IV.C.1-IV.C.2. Moreover, the light scattering techniques employed by Frei would not detect aggregates with the same level of precision as the DLS analysis of claim 5 or the microfiltration and product recovery analysis of claim 6. *Supra* §IV.C.3.c; Davies, ¶¶153-157.

The Petition makes the conclusory statements that "only routine optimization of the known stabilization factors in Frei's D-1 composition would be required to obtain an average AAV Rh <20 nm" for claim 5 (Petition, 60); and "to improve recovery following filtration through a 0.22μm filter, only routine optimization of the known stabilization factors already contained therein would be needed to reduce any residual aggregation" for claim 6 (Petition, 61). As explained above, however, there was no guidance in the prior art that suggested that adjusting elements of the composition, such as ionic strength, would result in a composition without substantial aggregation. *Supra* §IV.A.2.a (Ground 1), IV.C.2.a (Ground 3); Davies, ¶¶151-152. The inventors' solution to a long-time problem "is only straightforward in hindsight" based on the teachings of the '542 patent. *Leo Pharm.*, 726 F.3d at 1355. Accordingly, Novartis has failed to establish claims 5 and 6 as obvious under Ground 3.

V. THE BOARD SHOULD DENY THE PETITION UNDER *FINTIV* AND §314(a)

The Board should exercise its discretion to deny institution of the Petition under *Fintiv* and 35 U.S.C. §314(a). *See Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential) ("*Fintiv*"); *NHK Spring Co., Ltd. v. Intri-Plex Techs. Inc.*, IPR2018-00752, Paper 8 (PTAB Sep. 12, 2018) (precedential). As noted in *General Plastic Industrial Co. v. Canon Kabushiki Kaisha*, when "exercising discretion under 35 U.S.C. §314(a) and 37 C.F.R. §42.108(a), we are mindful of the goals of the AIA—namely, to…make the patent system *more efficient*…." IPR2016-01357, Paper 19 at 16 (PTAB Sept. 6, 2017).

Institution would be highly inefficient. Novartis filed two IPR petitions challenging the same claims of the '542 patent, neither of which will reach an FWD before trial in the Litigation. *See* Ex. 2010, 2 (March 2024 trial date). Novartis has not provided a *Sotera* stipulation and intends to present the ***same issues*** to the district court first. Ex. 2011, 234-50. Claim construction briefing is complete, a *Markman* hearing was held, fact discovery will be complete by the end of June, and trial is only nine months away. Novartis delayed filing these IPRs for twelve months. Novartis's Petitions did not even address *Fintiv* or whether the challenges present compelling merits despite the scheduled March 2024 jury trial. These facts, combined with the weakness of Novartis's patentability challenges, support denying institution under *Fintiv*. None of the exceptions in the Director's

Interim Procedure for Discretionary Denials (June 21, 2022) ("IP") apply here. IP, 4-7.

A. Factor 1: No Stay Has Been Sought and None is Likely

Novartis has not sought a stay of the Litigation nor indicated that it intends to seek a stay. *See Mylan Labs. Ltd. v. Janssen Pharmaceutica NV*, IPR2020-00440, Paper 17 at 14 (PTAB Sept. 16, 2020) (*Fintiv* factor 1 "leans towards denial of institution" where facts "indicate that no stay is likely to be entered").

Judge Andrews is unlikely to grant a stay in view of the upcoming trial and advanced status of the case (*supra* §V; *infra* §V.C). *See Ansell Healthcare Prods. LLC v. Reckitt Benckiser LLC*, Case No. 1:15-cv-00915, ECF No. 105 (D. Del. Dec. 1, 2016) (Andrews, J.) (denying stay where "[n]o IPR is sought on two of the four asserted patents"); *see also Collabo Innovations, Inc. v. Sony Corp. et al.*, Case No. 1:15-cv-01094, ECF No. 43 (D. Del. Jan. 5, 2017) (Andrews, J.) (denying stay where "fourth patent … will have to be litigated regardless"). Factor 1 weighs against institution.

B. Factor 2: The Proximity of Trial Weighs Against Institution

"If the court's trial date is earlier than the projected statutory deadline, the Board generally has weighed this fact in favor of exercising authority to deny institution …." *Fintiv* at 9. A five-day jury trial is scheduled to begin on March 25, 2024. Ex. 2010, 2. The Final Written Decision ("FWD") in this case (if

instituted) would not be expected until September 2024. *See* 35 U.S.C. §§314(b)(1), 316(a)(11). The jury will reach its verdict well before the Board's FWD. The March 2024 trial date is unlikely to change,[6] but even if moved, trial will likely conclude long before September 2024. *See Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 15 at 13 (May 13, 2020) (informative) ("*Fintiv II*") ("We generally take courts' trial schedules at face value absent some strong evidence to the contrary."). Factor 2 weighs against institution. *Fintiv II* at 13 (factor 2 favors discretionary denial where "trial is scheduled to begin two months before [the] deadline to reach [FWD].").

The result is similar if the Board "consider[s] the median time from filing to disposition," which is 32 months in the District of Delaware. *See* Ex. 2012; Ex. 2013, 14 (36.3 months in all civil cases). Thirty-two months from the filing of the complaint would be August 2024, still before the expected FWD.

C. Factor 3: The Parties' Significant and Continuing Investment in the Litigation Weighs Against Institution

Factor 3, considering "the amount and type of work already completed in the parallel litigation by the court and the parties at the time of the institution decision"

[6] Judge Andrews denied Genzyme's request to add a patent into the suit because of a potential for "substantial delay," illustrating that Judge Andrew's intent to not delay the district court proceedings. Ex. 2014.

weighs heavily in favor of denial. *Fintiv* at 9-10. The claim constructing hearing was held in April 2023 (*Genzyme Corporation et al v. Novartis Gene Therapies, Inc. et al.*, Case No. 1:21-cv-01736, D.I. 177 (D. Del. May 5, 2023)), fact discovery is scheduled to be completed in June 2023, and opening expert reports will be served August 4, 2023. Ex. 2010, 2. Genzyme served infringement contentions, and Novartis served its amended invalidity contentions, which raise the same arguments and art in this Petition in October 2022. Ex. 2011, 242-49 (asserting "Evans (2001) alone or in combination with" "Huang," "Wright", and "Mingozzi"), 234-41 (asserting "Frei (1999) alone or in combination with" "Huang" and "Mingozzi."). When the Board makes an institution decision, fact discovery will be complete and expert discovery nearly complete. Ex. 2010, 2.

Moreover, Novartis was aware of each prior art reference at least as early as October 2022 (Ex. 2011).[7] Regardless, Novartis waited to file the Petition for four months until February 2023, the day before expiration of the one-year § 315(b) bar. *See F5 Networks, Inc. v. WSOU Investments, LLC et al.*, IPR2022-00238, Paper No. 11 at 10 (PTAB May 19, 2022) (Factor 3 "additionally consider[s] whether Petitioner unreasonably delayed in filing the Petition.").

[7] Novartis served its amended invalidity contentions on October 11, 2022— then waited four months to file this Petition. *See* Ex. 2011, 279.

"Based on the level of investment and effort already expended on claim construction and invalidity contentions in the District Court," inluding over 660,000 pages of document productions, discovery requests, responses, and disputes, *Fintiv* factor 3 heavily favors discretionary denial. *Fintiv II* at 14; *see also Samsung Elecs. Co., Ltd. v. California Inst. of Tech.*, IPR2023-00133, Paper 10 at 15 (PTAB May 4, 2023) (factor 3 favors denial where the "scheduling order . . . indicates that Petitioner should have already served its opening expert report on validity.").

D. Factor 4: The Overlap in Issues Favors Non-Institution

"*Fintiv* requires that [the Board] consider whether 'the patentability disputes before the [district court] will resolve all or substantially all of the patentability disputes between the parties.'" *SK Innovation Co., Ltd. v. LG Chem, Ltd.*, IPR2020-00991, Paper 14 at 16 (PTAB Nov. 30, 2020). Novartis does not contend the grounds raised here are any different from those asserted in the district court. Nor could it. *Supra* §V.C; Ex. 2011, 234, 242.

Novartis has not offered a stipulation to not pursue in the Litigation Grounds it raised or reasonably could have raised in its Petitions. *See Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 (PTAB Dec. 1, 2020) (precedential as to §II.A)). Because Novartis raises the same arguments and art and has failed to provide a *Sotera*-type stipulation, this factor weighs in favor of denial.

E. Factor 5: The Identical Nature of the Parties Favors Non-Institution

Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation are Petitioners and the only defendants in the Litigation. Genzyme Corp. is the Patent Owner and a plaintiff in Litigation. This favors denial. *Fintiv* at 6; *Samsung Electronics Co., Ltd. v. California Institute of Technology*, IPR2023-00130, Paper 10 at 20 (PTAB May. 04, 2023) (fifth factor weighs against institution where petitioner "is a defendant in the Underlying Litigation.").

F. Factor 6: Other Circumstances

Because *Fintiv* factors 1-5 favor discretionary denial, the Board must consider whether the Petition presents a challenge with compelling merits. For compelling merits, the Board considers whether the "evidence, if unrebutted in trial, would plainly lead to a conclusion that one or more claims are unpatentable by a preponderance of the evidence." *Id.* at 4. "A challenge can only 'plainly lead to a conclusion that one or more claims are unpatentable' if it is highly likely that the petitioner would prevail with respect to at least one challenged claim." *OpenSky Indus., LLC v. VLSI Tech. LLC,* IPR2021-01064, Paper 102 at 49 (PTAB Oct. 4, 2022). The "compelling-merits challenge is a higher standard than the reasonable likelihood required for the institution of an IPR under 35 U.S.C. § 314(a)." *Id*., 49-50; *see also Commscope Techs LLC v. Dali Wireless, Inc.*, IPR2022-01242, Paper 23 at 3 (PTAB Feb. 27, 2023).

Here, the merits are weak and fall far short of "compelling." No ground is "sufficiently strong to override the concerns about duplication of effort by the Board and the district court." *See Immersion Sys. LLC v. Midas Green Techs., LLC*, PGR2021-00104, Paper 15 at 16-17 (PTAB Jan. 31, 2022). Thus, the *Fintiv* factors all favor discretionary denial, and the Board should exercise its §314(a) discretion to deny institution.

VI. CONCLUSION

For the foregoing reasons, the Petition should be denied, and no proceeding instituted.

Respectfully submitted,

Dated: June 15, 2023

/ Blaine M. Hackman /
Blaine M. Hackman, Ph.D.
Reg. No. 67,479
Counsel for Patent Owner

WORD COUNT CERTIFICATION

Pursuant to 37 C.F.R. § 42.24(d), I certify that this Preliminary Response contains 13,986 words (excluding the title page, table of contents, table of exhibits, this certificate, and the certificate of service), as determined by Microsoft Word.

Dated: June 15, 2023

/ Blaine M. Hackman /
Blaine M. Hackman, Ph.D.
Reg. No. 67,479
Counsel for Patent Owner

CERTIFICATE OF SERVICE

I certify that today in:

Novartis Gene Therapies, Inc. & Novartis Pharmaceuticals Corporation v. Genzyme Corporation, IPR2023-00608 (U.S. Patent 9,051,542)

I caused to be served a copy of:

PATENT OWNER'S PRELIMINARY RESPONSE
EXHIBITS 2004-2015

upon:

Novartis Gene Therapies, Inc. & Novartis Pharmaceuticals Corporation, c/o
John D. Livingstone, john.livingstone@finnegan.com
Amanda K. Murphy, Amanda.murphy@finnegan.com
Yieyie Yang, yieyie.yang@finnegan.com
M. David Weingarten, m.david.weingarten@finnegan.com
Cora Holt, cora.holt@finnegan.com
Christopher Weber, christoper.weber@finnegan.com

via:

electronic service to the email addresses above.

Dated: June 15, 2023

By: */Blaine M. Hackman/*

Blaine Hackman, Reg. No. 67,479
Dechert LLP
Three Bryant Park
1095 Avenue of the Americas
New York, NY 10036-6797
Tel: 212-698-3500
Fax: 212-698-3599
Blaine.hackman@dechert.com